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(54) Title: PHOSPHORIC ACID SALT OF 5-[[4-[2-(5-ETHYL-2-PYRIDINYL) ETHOXY] PHENYL] METHYL]-2, 4-THIAZOLIDINEDIONE

(57) Abstract: Phosphoric acid salt of 5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]- 2,4- thiazolidinedione is novel and exhibits, blood sugar-lowering activity in mammals and is of value as a prophylactic and/or therapeutic agent for prevention and/or treatment of diabetes.

TITLE OF THE INVENTION

PHOSPHORIC ACID SALT OF 5-[[4-[2-(5-ETHYL-2-PYRIDINYL) ETHOXY] PHENYL] METHYL]- 2,4-THIAZOLIDINEDIONE

FIELD OF THE INVENTION

The present invention relates to a novel compound and to a novel process for preparing the compound, to a pharmaceutical composition containing the compound and to the prophylactic and/or therapeutic use of the compound and composition.

BACKGROUND OF THE INVENTION

US 4,687,777 discloses 5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]- 2,4- thiazolidinedione. The compound exhibits blood-glucose and blood-lipid lowering action with lower toxicity, and may be safely administered, orally or parenterally, as it is or advantageously as a pharmaceutical composition comprising an effective amount of the compound or its pharmacologically acceptable salt and a pharmacologically acceptable carrier, excipient or diluent therefor, in the form of powder, granule, tablet, hard capsule, soft capsule, dry syrup, suppository, injection or the like.

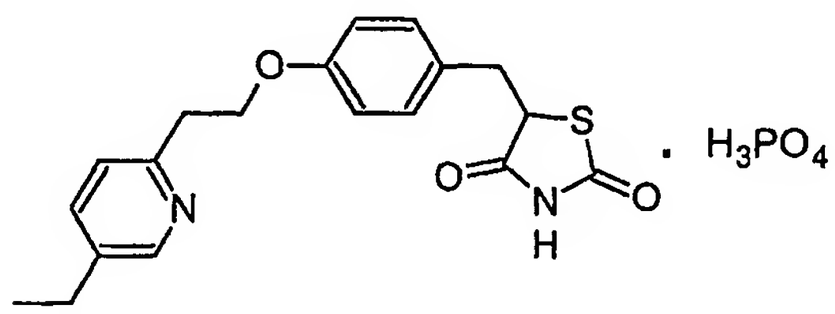
Hydrochloric acid salt of 5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]- 2,4- thiazolidinedione is currently marketed for treatment of Type II diabetes.

The present invention discloses a novel salt of 5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]- 2,4- thiazolidinedione namely phosphoric acid salt of 5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]- 2,4- thiazolidinedione which is useful in

the treatment of Type II diabetes. This compound shows good water solubility and good stability in solid form. Also this compound is significantly more soluble than the free base as well as the currently marketed HCl salt of 5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]- 2,4- thiazolidinedione.

SUMMARY OF THE INVENTION

The present invention relates to a novel compound, phosphoric acid salt of 5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]- 2,4- thiazolidinedione (FORMULA I), to a novel process for preparing the compound, to a pharmaceutical composition containing the compound and to the prophylactic and/or therapeutic use of the compound and composition.



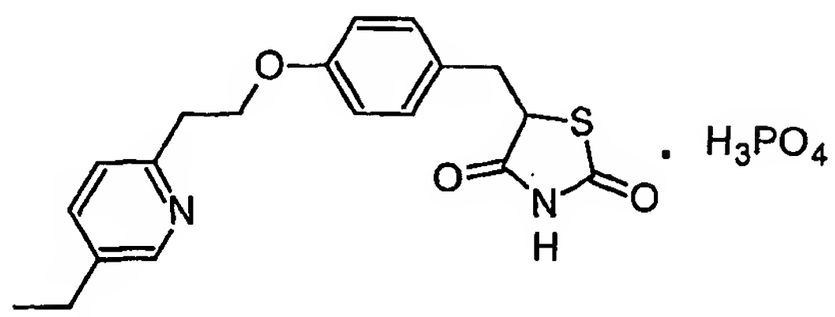
FORMULA I

The present invention provides a compound of formula I or a tautomeric form thereof, for use in the treatment of and/or prophylaxis of hyperglycemia.

The surprising and advantageous stability and water solubility of this compound provides for significant formulation and bulk handling advantages.

DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention provides a novel compound of formula I



FORMULA I

or a tautomer thereof.

The compound of formula I is a phosphoric acid salt of 5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]- 2,4-thiazolidinedione.

As stated the compound of the invention is significantly more soluble in water than the corresponding free base or currently marketed HCl salt. A convenient method for determining the stability of the compounds of the invention in aqueous solution involves determining the degree of precipitation of the parent free base from an aqueous solution of the test compound at known conditions of temperature and over known periods of time. We have found that the compound of formula I show good stability in aqueous conditions.

The currently marketed HCl salt of 5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]- 2,4- thiazolidinedione is practically insoluble in water (The Merck Index Online, 2003). The compound of present invention is freely soluble in water. This has significant pharmacokinetic advantage.

The quantitative analysis of the test may be carried out using conventional methods e.g. HPLC.

As mentioned above the compound of the invention is indicated as having useful therapeutic properties.

The present invention accordingly provides a compound of formula I, and/or a tautomeric form, for use as an active therapeutic substance.

Thus the present invention provides a compound of formula I, or a tautomeric form thereof, for use in the treatment of and/or prophylaxis of hyperglycemia.

Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of formula I, or a tautomeric form thereof, and a pharmaceutically acceptable carrier therefor.

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycemia in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula I, or a tautomeric form

thereof, to a hyperglycemic human or non-human mammal in need thereof.

The reaction between the compound of formula I and the source of phosphoric acid counter-ion is generally carried out under conventional salt forming conditions, for example by admixing the compound of formula I and the source of counter-ion, phosphoric acid, suitably in approximately equimolar amounts but preferably using an excess of the source of counter-ion, phosphoric acid, in a solvent, generally a C1-4 alkanolic solvent such as methanol, ethanol, or other aprotic solvents like acetonitrile, at any temperature which provides a suitable rate of formation of the required product, generally at an elevated temperature and thereafter isolating the product.

The following Example illustrates the invention but does not limit it in any way.

EXAMPLES

Example 1

PHOSPHORIC ACID SALT OF 5-[[4-[2-(5-ETHYL-2-PYRIDINYL) ETHOXY] PHENYL] METHYL]- 2,4-THIAZOLIDINEDIONE

A suspension of 5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]- 2,4- thiazolidinedione base (5 g, 0.014 mol) in methanol (50 ml) was heated to 50-60°C and phosphoric acid (85%, 11.3 ml) was added. After stirring for 30 minutes at the same temperature, the reaction mixture was concentrated to about 10 ml and chilled to afford title compound.

Example 2

PHOSPHORIC ACID SALT OF 5-[[4-[2-(5-ETHYL-2-PYRIDINYL) ETHOXY] PHENYL] METHYL]- 2,4-THIAZOLIDINEDIONE

A suspension of 5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]- 2,4- thiazolidinedione base (100 g, 0.28 mol) in acetonitrile (500 ml) was heated to 50-60°C and phosphoric acid (85%, 150 ml) was added. After stirring for one hour at the same temperature, the reaction mixture was concentrated to about 250 ml and chilled to afford title compound.

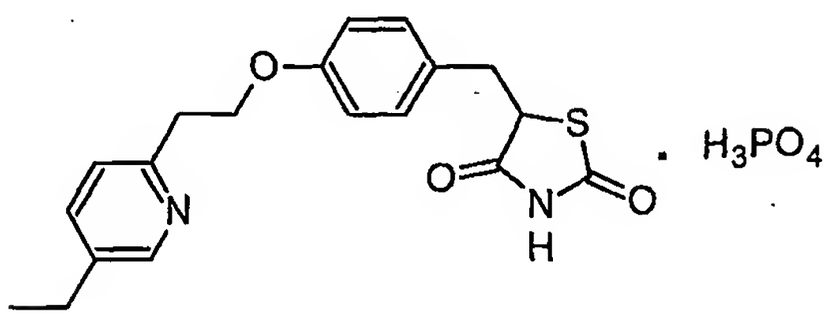
Example 3

PHOSPHORIC ACID SALT OF 5-[[4-[2-(5-ETHYL-2-PYRIDINYL) ETHOXY] PHENYL] METHYL]- 2,4-THIAZOLIDINEDIONE

A suspension of 5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]- 2,4- thiazolidinedione base (100 g, 0.28 mol) in isopropyl alcohol (750 ml) was heated to 50-60°C and phosphoric acid (85%, 150 ml) was added. After stirring for one hour at the same temperature, the reaction mixture was concentrated to about 250 ml and chilled to afford title compound.

We claim

1. A compound of formula I



FORMULA I

or tautomeric form thereof.

2. A compound according to claim 1, which is phosphoric acid salt of 5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]- 2,4- thiazolidinedione.

3. A process for the preparation of compound I of claim 1, comprising

contacting the 5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]- 2,4- thiazolidinedione free base with phosphoric acid.

4. A process as in claim 3, wherein the reaction is carried out in a solvent selected from water miscible solvent or water immiscible solvent.

5. A process as in claim 4, wherein the solvent is water miscible.

6. A process as in claim 5, wherein the solvent is a linear or branched alkanol or acetonitrile.

7. A process as in claim 6, wherein the alkanol is selected from methanol, ethanol or isopropyl alcohol.

8. A process as in claim 3, wherein the reaction is carried out at a temperature between 25-100^{0}C.

9. A pharmaceutical composition comprising a prophylactically and/or therapeutically effective amount of the compound of claim 1.

10. A method of prevention and/or treatment of hyperglycemia comprising administering effective amount of compound of claim 1.

11. Use of compound of claim 1 as ingredient in the manufacture of medicament for use in the prevention and/or treatment of hyperglycemia.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN03/00295

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C07D 417/12; A61K 31/4439; A61P 3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN: File Registry: Molecular formula search based on compounds of Formula I; Espacenet: Keyword: Pioglitazone

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 4687777 A (MEGURO et al) 18 August 1987 See Especially Column 2 lines 15-23	1-11
Y	Remington: The Science and Practice of Pharmacy, Twentieth Edition, 2000, Philadelphia College of Pharmacy and Science, pages 703-704 See especially Table 38-2, page 704	1-11
A	WO 03/026586 A (TEVA PHARMACEUTICAL INDUSTRIES LTD) 3 April 2003	

☐ Further documents are listed in the continuation of Box C ☒ See patent family annex

* Special categories of cited documents:

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 December 2003	12 DEC 2003
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **R.L. POOLEY** Telephone No : (02) 6283 2242

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN03/00295

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member (To put a line under the citations tab to the first point on the next row and press F8)					
US	4687777	AU	572719	CA	12773232	DE	3662689
		EP	193256	JP	61/267580		
WO	03/025586	US	2003139603				
							END OF ANNEX

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